REMARKS

Applicant requests reconsideration of the application in view of the discussion that follows. The status of the claims is as follows. Claims 41-97 were previously canceled without prejudice to Applicant's filing of divisional applications to the separately patentable subject matter thereof and claims 3, 4, 26 and 98-101 were previously canceled and claims 148-165 were added previously. Claims 1, 2, 5-25, 27-40 and 102-165 are pending. Claims 1, 2, 11, 102, 122, 123, 146, 148, 157 and 158 have been amended herein.

The Amendment

Claim 1 was amended to recite the step of outputting results of the selecting in a machine-readable and/or a human-readable form. Support therefor is in the specification, for example, page 56, line 30.

Claims 2 and 11 were amended to refer to the number of oligonucleotides in the clusters of oligonucleotides. Support therefor is in the specification, for example, page 40, lines 20-21.

Claim 102 was amended to recite the step of outputting results of the selecting in a machine-readable and/or a human-readable form. Support therefor is in the specification, for example, page 56, line 30. Claim 102 was also amended to refer to the number of oligonucleotides in the clusters of oligonucleotides. Support therefor is in the specification, for example, page

Claim 122 was amended to recite the step of outputting results of the selecting in a machine-readable and/or a human-readable form. Support therefor is in the specification, for example, page 40, lines 20-21.

Claim 23 was amended to refer to the number of oligonucleotides in the clusters of oligonucleotides. Support therefor is in the specification, for example, page 40, lines 20-21.

Claim 146 was amended to correct a typographical error in step (d).

Claim 148 was amended in a manner similar to that for claim 102 above.

Claim 157 was amended to recite the step of outputting results of the selecting in a machine-readable and/or a human-readable form. Support therefor is in the specification, for example, page 56, line 30.

Claim 158 was amended to refer to the number of oligonucleotides in the clusters of oligonucleotides. Support therefor is in the specification, for example,

page 40, lines 20-21.

Rejection under 35 U.S.C. §112

Claims 2, 11, 39, 40, 102-121, 123, 142-143, 148-156, and 158 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action contends that claims 2, 11, 39, 40, 102-121, 123, 142-143, 148-156, and 158 each have a step of ranking oligonucleotide clusters based on their size. However, it is unclear and ambiguous as to whether the clusters are ranked based on how many members of the cluster exist, or whether the clusters are ranked based on the oligonucleotide size (number of base pairs or length of each oligonucleotide within the cluster).

Applicant submits that the amendments to claims 2, 11, 102, 123, 148 and 158 obviate the above grounds of rejection with regard to these claims.

Applicant respectfully traverses the above rejection of claims 39, 40 and 142-143. These claims include the language "determining the sizes of said clusters of step (d) by counting the number of contiguous oligonucleotides in said region of said hybridizable sequence." (emphasis added) As can be seen, the claims already refer to the number of oligonucleotides with regard to the sizes of the clusters.

Rejection under 35 U.S.C. §§112 and 101

Claims 1, 2, 4, 25, 27-40, 102-145, and 148-165 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant submits that the above amendments to claims 1, 102, 122, 148 and 157 obviate this ground of rejection.

Claims 1, 2, 4-25, 27-40, 102-145, and 148-165 were rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Applicant submits that the above amendments to claims 1, 102, 122, 148 and 157, which now includes the step of outputting results in human-readable and/or machine-readable form, obviate this ground of rejection.

Rejection under 35 U.S.C. §103

Claims 1-2, 11-12, 16-22, 28-29, 37, 39, 40, 102-104, 106-108, 110-112, 119-

121, 122-124, 126-128, 130-132, 139-141, 148-151, and 154-156 were rejected under 35 U.S.C. 103(a) as being unpatentable over Southern, *et al.* (Nucleic Acids Research, 1994, volume 22, pages 1368-1373) (Southern 1) in view of Southern (Current Opinion in Biotechnology, 1996, volume 7, pages 85-88) (Southern 2).

Southern 1 discloses a method for making arrays of oligonucleotides corresponding to a full set of complements of a known sequence in a single series of base couplings in which each base in the complement is added in turn. Coupling is carried out on the surface of a solid support such as a glass plate using a device that applies reagents in a defined area. The device is displaced by a fixed movement after each coupling reaction so that consecutive couplings overlap only a portion of previous ones. The shape and size of the device and the amount by which it is displaced at each step determines the length of the oligonucleotides. Certain shapes create arrays of oligonucleotides from mononucleotides up to a given length in a single series of couplings. The array is used in a hybridization reaction to a labeled target sequence and shows the hybridization behavior of every oligonucleotide in the target sequence with its complements in the array.

Southern 2 discusses techniques and applications of high-density gridding. The reference states that there are basically two different types of arrays, namely, general purpose arrays and dedicated arrays. The general purpose arrays comprise all sequences of a given length that can be employed to analyze sequences for which no previous sequence information is available. The dedicated or scanning arrays represent the oligonucleotides complementary to a target of known sequence.

The Office Action refers to (and quotes) several passages from Southern 1, namely, the abstract, the legend for Figure 3, and page 87, column 2, lines 4-7, and from Southern 2, namely, page 87, paragraph bridging columns 1 and 2. The cited and quoted passages from Southern 2, the Office Action alleges, offer a thorough synopsis of the original article (referring to Southern 1).

None of the cited passages of Southern 1 and/or Southern 2, either individually or in combination, disclose or suggest each and every element of claim 1. The combination of the teachings of the references fails to disclose or suggest at least the following elements of claim 1: (i) identifying a predetermined number of non-identical oligonucleotides within a nucleotide sequence that is hybridizable with said target nucleotide sequence, said oligonucleotides being chosen to sample a length of said nucleotide sequence, wherein said non-identical oligonucleotides are

of identical length N and are spaced one nucleotide apart, said predetermined number comprising L-N+1 oligonucleotides, where L is the length of the hybridizable sequence, (ii) selecting a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides based on an examination of said parameter, (iii) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence and (iv) selecting, for a cluster, a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster.

The Office Action alleges that Figures 3 and 4 of Southern 1 illustrate the experimental and computational analysis of the results on pages 1371 and 1372, respectively, of the reference. The Office Action contends that the parameter in Figure 3c indicating extent of hybridization is the color of each ring with respect to the others (i.e., a darker ring represents greater hybridization intensity). Based on this parameter, argues the Office Action, several clusters of darker colors are present in Figure 3c. Figure 3c, continues the Office action, also illustrates (through numbers with arrows) specific oligonucleotides in the subsets that are hybridizable to the target nucleotide sequences (referring to the caption to Figure 3 on page 1371 of Southern 1). Consequently, concludes the Office Action, the caption and its illustration indicates qualitative ranking between clusters based on both cluster size and lengths of oligonucleotides within the clusters. The Office Action further alleges that subsets of the clusters are selected with the numbered arrows above the picture. The oligonucleotides can be DNA or RNA and they are parts of microarrays as indicated in the title of Southern 1.

The Office Action recognizes that Southern 1 does not teach the step of predicting the hybridization of the oligonucleotide by the presence of the hybridization cluster. However, asserts the Office Action, Southern 2 states in the section on page 87, column 2, lines 4-7, "It is envisaged that dedicated arrays will be useful for mutation detection. Comparison of the hybridization patterns of wild-type and mutant sequences to an array of oligonucleotides complementary to the wild type will reveal a difference." It would have been obvious to someone of ordinary skill in the art at the time of the instant invention, concludes the Office Action, to modify the complementary arrays of Southern 1 with the mutation detection method of Southern 2 because, alleges the Office Action, while both methods use the same

method of staggered hybridization, and the senior study cites the junior study as its method of use, Southern 2 has the advantage of employing the techniques of Southern 1 for mutation analysis.

Applicant respectfully traverses the above grounds of rejection. First, claim 1, step (a) refers to non-identical oligonucleotides of identical length N. On the other hand, as recognized in the Office Action and taught in Southern 1, the oligonucleotides of the reference represent a number of oligonucleotides of different lengths (see, for example, Southern 1, page 1373, column 1, lines 40-43 and 47-50, and column 2, lines 1-3). As is evident from the disclosure of the reference, the arcs or crescents, which the Office Action equates to clusters of the present claims, comprise oligonucleotides of many different lengths.

The combined teachings of the references do not disclose or suggest selecting a subset of oligonucleotides within a predetermined number of non-identical oligonucleotides based on an examination of a parameter. As is evident from the concluding sentence of the article, the array method presented by Southern 1 provides an empirical method for analyzing the interactions of a target molecule with a complete set of complementary oligonucleotides. Therefore, as evidenced by the clear teaching of the references, no selection of a subset of oligonucleotides is made.

The conclusion in the Office Action that the caption and its illustration (referring to Southern 1, Figure 3) indicates qualitative ranking between clusters based on both cluster size and lengths of oligonucleotides within the clusters is not supported by the teaching of the reference. As can be seen at the bottom of column 1 on page 1373, the arcs or crescents are merely areas in which longer and shorter oligonucleotides hybridize to the target. No selection process is made. The further allegation in the Office Action that subsets of the clusters are selected with the numbered arrows above the picture does not correspond to the elements of claim 1 that recite (iii) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence and (iv) selecting, for a cluster, a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster. The numbered arrows in Figure 3c of Southern 2 do not represent a selection process as presently claimed. It appears that the numbered arrows merely identify positions where oligonucleotides of various

lengths interact with the target. Furthermore, the concluding remark of Southern 1 that indicates that a complete set of complementary oligonucleotides is employed substantiates the fact that Southern 1 is not making any selection, particularly as presently claimed.

As a result of the present invention, only a small fraction of the potential oligonucleotide probe candidates are synthesized and tested. As noted in Applicant's specification, this is in sharp contrast to the known method of synthesizing and testing all or a major portion of potential oligonucleotide probes for a given target sequence (specification, page 42, line 28). Such an approach is particularly important in the area of array analysis of target nucleotide sequences. As explained in the specification (page 5, lines 17-28), oligonucleotide arrays can contain hundreds of thousands of different sequences and conditions are chosen to allow the oligonucleotide with the lowest melting temperature to hybridize efficiently. These conditions are usually relatively non-denaturing and secondary structure constraints become significant. Arrays are generally utilized under relatively non-denaturing conditions in contrast to, for example, PCR conditions, which tend to be strongly denaturing.

There is no recognition in the combined teachings of the references to perform parameter analysis and then to view the oligonucleotides for clusters along the target sequence. In the approach of the invention all of the oligonucleotides are viewed according to order of position along the target sequence to determine the number of oligonucleotides that are clustered, i.e., the number of oligonucleotides from the point along the nucleotide sequence just after a rejected set of oligonucleotides to the point along the nucleotide sequence of the next set of oligonucleotides rejected by the parameter analysis. The greater the number of oligonucleotides present in the cluster, the higher the potential that the oligonucleotides will hybridize to the target nucleotide sequence. Such oligonucleotides are selected for further analysis. For reasons presented above, the combined teachings of Southern 1 and Southern 2 do not disclose or suggest such an approach.

The Office Action asserts that it would be obvious to use the numerical parameters and ranges as described in claims 27 and 28 as they are obvious variants of the conventionally employed methods. This statement in the Office Action is pure speculation unsupported by any reference. Claim 27 is directed to the

present method and further comprises optimizing according to calculation for said parameter based on said individual scores. Claim 28 depends from claim 1 and further in step (b) comprises determining at least two parameters wherein the absolute value of a correlation coefficient between said parameters is less than 0.5. In any event, claims 27 and 28 depend ultimately from claim 1 and are therefore patentable over the combined teachings of Southern 1 and Southern 2 by virtue of such dependency since claim 1 is patentable over the combined teachings as demonstrated above.

Claims 1, 11, 13-14, 122, 126, 128, and 148-149 were rejected under 35 U.S.C. 103(a) as being unpatentable over Southern 1 in view of Southern 2 as applied to claims 1-2, 11-12, 16-22, 28-29, 37, 39, 40, 102-104, 106-108, 110-112, 119-121, 122-124, 126-128, 130-132, 139-141, 148-151, and 154-156 above, and further in view of Southern, *et al.* (Genomics, 1992, volume 13, pages 1008-1017) (Southern 3). The Office Action asserts that, while Southern 1 in view of Southern 2 teach the methods of claims 1-2, 11-12, 16-22, 28-29, 37, 39, 40, 102-104, 106-108, 110-112, 119-121, 122124, 126-128, 130-132, 139-141, 148-151, and 154-156, they do not teach the method of statistical sampling with dimensionless numbers as required by the instant claims. The Office Action further contends that Southern 3 illustrates, on page 1013 in Tables 1 and 2, ranks of clusters illustrated in Figure 5 on page 1013 of Southern 3 and further contends that Southern 3 ranks the clusters and provides dimensionless scores of sequences within each cluster. It would have been obvious at the time of the instant invention, contends the Office Action, to modify Southern 1 in view of Southern 2 as applied to claims 1-2, 11-12, 16-22, 28-29, 37, 39, 40, 102-104, 106-108, 110-112, 119-121, 122-124, 126-128, 130-132, 139-141, 148-151, and 154-156 above, in further view of Southern 3 to result in the instant invention because Southern 3 has the advantage of quantitative ranking for more efficient genomic analysis.

Applicant respectfully traverses the above ground of rejection. Southern 3 discloses a method for making complete sets of oligonucleotides of defined length, covalently attached to the surface of a glass plate, by synthesizing them *in situ*. A device carrying all octapurine sequences was used to explore factors affecting molecular hybridization of the tethered oligonucleotides, to develop computer-aided methods for analyzing the data and to test the feasibility of using the method for sequence analysis. Southern 3 notes that further development is needed before the

method can be used routinely.

In view of the comments in the reference concerning further development, it would not have been obvious to one skilled in the art to make the substitution of teachings as alleged in the Office Action particularly where the skilled artisan would have any expectation of success in making the combination. Furthermore, the ranking conducted in the reference is not that recited in claim 2, for example. In claim 2 the oligonucleotides are ranked based on the number of oligonucleotides in the clusters of oligonucleotides. In Southern 3, each oligonucleotide in the list of oligonucleotides is ranked; there is no ranking based on the size of a cluster. As a matter of fact, there is no teaching in the reference of a cluster of oligonucleotides as presently claimed. Finally, Southern 3 discloses making complete sets of oligonucleotides.

The statement in the Office Action that it would be further obvious to determine the quartile of the intensities of each of the hybridizable oligonucleotides as each hybridizable nucleotide is a member of a quartile... is unclear and unsupported in any reference.

Applicant submits that the combined teachings of the references are deficient because of the lack of a teaching or suggesting of claimed features of claims 13, 14, 128 and 149, which claim statistically sampling a cluster of oligonucleotides, and claims 25 and 27, which claim use and optimization of dimensionless numbers to score the ranks of hybridization. In any event, the claims depend from claims that are patentable over the combined teachings of the references as demonstrated above and are, therefore, patentable over the combined teachings at least on the basis of such dependency.

Claims 1, 10, 15, 102, 109, 122, 129, 142, 143-145, 146-148, and 153 were rejected under 35 U.S.C. 103(a) as being unpatentable over Southern 1 in view of Southern 2 as applied to claims 1-2, 11-12, 16-22, 28-29, 37, 39, 40, 102104, 106-108, 110-112, 119-121, 122-124, 126-128, 130-132, 139-141, 143, 145, 148-151, and 154-156 above, and further in view of Drmanac, *et al.* (Genomics, volume 4, pages 114-128, 1989) (Drmanac).

Without acquiescing in the assertions in the Office Action, Applicant submits that the claims depend from claims that are patentable over the combined teachings of the references as demonstrated above and are, therefore, patentable over the combined teachings at least on the basis of such dependency. Drmanac does not

cure the deficiencies of the primary references.

Claims 1, 5-7, 23-24, 30-36, 38, 102, 105, 113-118, 122, 125, 133-138, 148, 152, 157-162, 164-165 were rejected under 35 U.S.C. 103(a) as being unpatentable over Southern 1 in view of Southern 2 as applied to claims 1-2, 11-12, 16-22, 28-29, 37, 39, 40, 102-104, 106-108, 110-112, 119-121, 122-124, 126-128, 130-132, 139-141, 148-151, and 154-156 above, and further in view of Petersheim, *et al.* (Biochemistry, 1983, volume 22, pages 256-263) (Petersheim).

Without acquiescing in the assertions in the Office Action, Applicant submits that the claims depend from claims that are patentable over the combined teachings of the references as demonstrated above and are, therefore, patentable over the combined teachings at least on the basis of such dependency. Petersheim does not cure the deficiencies of the primary references.

Claims 157 and 163 were rejected under 35 U.S.C. 103(a) as being unpatentable over Southern 1 in view of Southern 2 in view of Petersheim as applied to claims 1, 5-7, 23-24, 30-36, 38, 102, 105, 113-118, 122, 125, 133-138, 148, 152, 157-162, 164-165 above, and further in view of Drmanac.

Without acquiescing in the assertions in the Office Action, Applicant submits that the claims depend from claims that are patentable over the combined teachings of the references as demonstrated above and are, therefore, patentable over the combined teachings at least on the basis of such dependency. Drmanac does not cure the deficiencies of the primary references.

Claims 1 and 8-9 were rejected under 35 U.S.C. 103(a) as being unpatentable over Southern 1 in view of Southern 2 as applied to claims 1-2, 11-12, 16-22, 28-29, 37, 39, 40, 102-104, 106-108, 110-112, 119-121, 122-124, 126-128, 130132, 139-141, 143, 145, 148-151, and 154-156 above, and further in view of McMahon, *et al.* (U.S. Patent No. 5,310,650) (McMahon).

Without acquiescing in the assertions in the Office Action, Applicant submits that claims 8 and 9 depend from claim 1, which is patentable over the combined teachings of the references as demonstrated above and are, therefore, patentable over the combined teachings at least on the basis of such dependency. McMahon does not cure the deficiencies of the primary references.

Double Patenting

Applicant acknowledges the indication in the Office Action that the Terminal

Disclaimer, which was submitted with Applicant's previous response, obviates this ground of rejection.

Conclusion

Applicant submits that claims 1, 2, 4-25, 27-40 and 102-165 satisfy the requirements of 35 U.S.C. §§101, 112 and 103. Allowance of the above-identified patent application, it is respectfully submitted, is in order.

Respectfully submitted,

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